Comments on E14 and S7B June guidelines

The ICH E14 guidance contains two points in the "design" section (2.1) that require clarification. First, the guidance indicates that a "thorough QT/QT_c clinical study" (TCS) will be conducted regardless of the outcome of non-clinical testing. This implies that the clinical study may be conducted without non-clinical data. Second, the guidance indicates that if non-clinical data are "informative enough" about the risk of QT prolongation, some regions (presumably Europe, Canada and Japan) may modify the requirements of the TCS. Thus, there will be regional differences in the conduct of TCSs that would defeat the purpose of the ICH.

We believe that non-clinical data must be obtained on all non-antiarrhythmic drugs before first use in man. Absent these data, the risk of not knowing that a drug might block hERG and prolong APD at submicromolar concentrations is simply too great. We also believe that the results of the non-clinical tests should affect the design of TCSs. A drug having no hERG, APD or QT signals non-clinically should satisfy a minimum TCS agreed upon by all ICH regions. A drug having these signals would be subjected to more stringent TCSs depending on the level of risk. A drug showing block in the hERG assay but no APD or QT signals should have a different TCS from a drug showing all three signals. Furthermore, TCSs should differ depending on the ratio of potency of the non-clinical signal to effective therapeutic plasma concentration (Redfern et al, 2003). A drug with a ratio below 30 should have a more stringent TCS than a drug with a ratio above 100. In summary, non-clinical studies are necessary before first use in man and differences among non-clinical results should guide the stringency of thorough QT/QTc clinical studies that will be done.

It follows that we do not agree with the June 04 S7B guidance statement indicating that assessment of the risk for delayed ventricular repolarization and QT interval prolongation *does not* need to be done prior to first use in humans. This statement conflicts with the S7A guidance stating that the effect of the test substance on the core battery systems should be investigated *prior* to first use in humans. In addition to this conflict between the S7A and S7B guidances, the S7B guidance contradicts itself in Section 2.4. Initially the guidance states that "results from S7B non-clinical studies assessing the risk for delayed ventricular repolarization and QT interval prolongation generally do not need to be available prior to first administration in humans;" whereas the last sentence in the same paragraph states that the "early availability of these data is considered valuable." If the data are valuable in risk evaluation, they should be collected and analyzed prior to first use in humans.

Another conflict between the S7A and the S7B is GLP status. The S7A states that the core battery safety testing should be done following GLP guidelines. The purpose of the GLP requirement is to enforce a uniformly high standard of scientific rigor for all submitted data. The S7B does not mention GLP requirements, implying that a lower standard is acceptable. This seems unjustified given the high level of concern for QT risk. Since 21 CFR Part 58 is applicable to all non-clinical data submitted to the FDA as part of an application, the S7B should require GLP studies.

A modification to the section in S7A section 2.7.2 dealing with the core battery and references to S7B on would change the last sentence in Section 2.7.2 to say “should be evaluated” instead of “should be considered.”